More specifically, the parent patent – U.S. 6,132,718 is a method of administering Tcells that contain vectors encoding the genes for the variable region of an Ab1 or an Ab2, stimulating the proliferation of the T cells and then administering Ab2-conjugated to a soluble immunogenic carrier or Ab1-conjugated to a soluble immunogenic carrier, respectively. Neither of these claims include a step of administering cytokines to the patient.

A review of the presently pending claims show that they are direct to the administration of the same T-cells with either the variable regions of Ab1 or Ab2 but additionally includes the administration of a cytokine after the administration of the transfected T cells. The Examiner's previous argument is that the claims of the patent require an additional step of a vaccine comprising an anti-idiotype antibody. Applicant respectfully disagree with this assessment. First, claim 1 of the '718 patent requires the anti-ID vaccine but claim 2 requires administration of the Ab1 vaccine. Whereas the claims in the present application, administer the transfected T-cells and then a cytokine. The specification discloses on page 30, lines 13-24, that the cytokine treatment can be used to amplify the immune response. The present claims provide another method different from the method in the '718 patent to enhance the efficacy of adoptive immunotherapy. Thus, the pending claims and the claims of the '718 patent are not obvious over each other and it is requested that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 48-57 remain rejected under 35 U.S.C. § 103(a) as obvious over Eshhar *et al.*, *Proc. Nat'l Acad. Sci. USA* **90:** 720 (1993), WO 92/15322, Wagner *et al.*, *Biotech. Therap.* **3:** 81 (1992), and "applicant's admission" at page 22 of the specification, in view of Hansen *et al.*, *Cancer* **71:** 3478 (1993) ("Hansen"). Applicant respectfully traverses this rejection.

The Examiner maintains her rejection of claims 48-57 for the same reasons as set forth in the previous Office Action and maintains her position that Eshhar suggests the use of chimeric genes in adoptive immunotherapy. The Examiner maintains her position that Eshhar and Wagner show that such chimeric genes can be used in diseases caused by either tumors or infectious agent, and that this motivation comes from Eshhar. The Examiner takes the position that both the Eshhar 1993 and 1990 publications show that different research groups induce the cellular arm of the immune system.

As discussed above in regard to the obvious-type double patenting rejection, the pending claims are directed to a method of inducing a cellular immune response against a TAA or against a disease caused by an infectious agent by administering transfected T cells and then at least one cytokine. The present invention specifically achieves this response in one of two ways:

Firstly, (1) transfected T cells are administered in an effective immunostimulatory amount are produced by obtaining T cells from the patient and transfecting these T cells with an expression vector containing a DNA molecule encoding either a chimeric immunoglobulin/T cell receptor or a chimeric immunoglobulin/CD3 protein, and wherein the immunoglobulin-encoding portion of the DNA molecule encodes the variable region of an antibody that binds with the TAA or with an antigen associated with the infectious agent, and further wherein the variable regions of the α and β polypeptide chains of said T cell receptor are replaced by the variable regions of the antibody; and then (2) at least one cytokine is adminstered.

Secondly, (1) transfected T cells are administered in an effective immunostimulatory amount are produced by obtaining T cells from the patient and transfecting these T cells with an expression vector containing a DNA molecule encoding either a chimeric immunoglobulin/T cell receptor or a chimeric immunoglobulin/CD3 protein, and wherein the immunoglobulin-encoding portion of the DNA molecule encodes the variable region of an antibody that mimics an epitope of the TAA or an epitope of an antigen associated with the infectious agent, and further wherein the variable regions of the α and β polypeptide chains of said T cell receptor are replaced by the variable regions of the antibody; and then (2) at least one cytokine is adminstered.

Neither Eshhar or Wagner disclose administering a cytokine after infusing the transfected T cells rather the Examiner appears to be arguing that Eshhar suggests that a cytokine, i.e., IL-2, is produced when the transfected T cells interact with the tumor. Applicant's specification on pages 25-30 discloses the preparation of the transfected T cells and the methods of using them to treat a patient. Particularly, page 30 lines 13-24 discloses methods to enhance the efficacy of adoptive immunotherapy. The administration of cytokines is performed after the administration of transformed T cells to amplify the immune response.

In this regard, the Examiner is referred to a number of post-published papers that support the amplification of the immune response with the subsequent administration of cytokines. For example, the Darcy *et al.* abstract demonstrate that added interferon (IFN-γ) enhances the effectiveness of T cells in an *in vitro* experiment. In this study, the anti-CEA antibody was grafted onto the FcR-gamma receptor. Further, an abstract of Aarts *et al.* discloses a study using the CEA tumor antigen and concludes that vaccine **in combination with cytokines**, may be essential to obtain the level of T-cell response directed against a self-antigen, such as CEA, that is necessary to achieve antitumor response.

The Examiner's arguments are directed to combining Eshhar and Wagner to make the transfected Tcells but as applicant noted above, the method requires the subsequent administration of at least one cytokine. Applicant submits that none of the prior art publications used in this obviousness rejection disclose administering a cytokine subsequent to the administration of the transfected T cells and nor do any of these publications provide a rationale for doing so. The cited post-published abstracts disclose, as stated in applicant's specification, that the subsequent administration of cytokines amplify the immune response. In view of these arguments, it is requested that this rejection of the pending claims be withdrawn.

CONCLUSION

Applicant kindly requests reconsider of the final rejection and entry of this response. The response does not raise any new issues and supports the disclosure in the specification of the purpose of the presently claimed methods of administering the transfected T cells and at least one cytokine. In view of the foregoing, it is respectfully urged that the present claims are in condition for allowance. An early notice to this effect is earnestly solicited. Should there be any questions regarding this application, the Examiner is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,

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